# PATENT COOPERATION TREATY



# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| | | |
|---|---|---|
| Applicant's or agent's file reference<br>010900-0005 | **FOR FURTHER ACTION** | See Form PCT/IPEA/416 |
| International application No.<br>PCT/CA2004/001470 | International filing date *(day/month/year)*<br>06 August 2004 (06-08-2004) | Priority date *(day/month/year)*<br>06 August 2003 (06-08-2003) |

International Patent Classification (IPC) or national classification and IPC
IPC: ***C07C 57/12*** (2006.01) , ***C11C 3/14*** (2006.01) , ***A61K 31/202*** (2006.01) , ***C07C 13/21*** (2006.01) , ***A61P 35/00*** (2006.01)

Applicant
UNIVERSITÉ LAVAL ET AL

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. [x] *(sent to the applicant and to the International Bureau)* a total of 7 sheets, as follows:
      [x] sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      [ ] sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. 1 and the Supplemental Box.
   b. [ ] *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))
      , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - [X] Box No. I Basis of the report
   - [x] Box No. II Priority
   - [x] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - [ ] Box No. IV Lack of unity of invention
   - [x] Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - [ ] Box No. VI Certain documents cited
   - [x] Box No. VII Certain defects in the international application
   - [ ] Box No. VIII Certain observations on the international application

| | |
|---|---|
| Date of submission of the demand<br>04 March 2005 (04-03-2005) | Date of completion of this report<br>10 February 2006 (10-02-2006) |
| Name and mailing address of the IPEA/CA<br>Canadian Intellectual Property Office<br>Place du Portage I, C114 - 1st Floor, Box PCT<br>50 Victoria Street<br>Gatineau, Quebec K1A 0C9<br>Facsimile No.: 001(819)953-2476 | Authorized officer<br>Maria Slaby (819) 997-2934 |

**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**

International application No.
PCT/CA2004/001470

**Box No. I Basis of the report**

1. With regard to the **language**, this report is based on:

[ x ] the international application in the language in which it was filed

[ ] a translation of the international application into , which is the language of a translation furnished for the purposes of:

[ ] international search (Rules 12.3(a) and 23.1(b))

[ ] publication of the international application (Rule 12.4(a))

[ ] international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

[ ] the international application as originally filed/furnished

[ x ] the description:

| | | | | |
|---|---|---|---|---|
| [ x ] | pages | 1 to 3, 5 to 41 | | as originally filed/furnished |
| [ x ] | pages* | 4, 42 to 45 | received by this Authority on | 18 July, 2005 |
| [ ] | pages* | | received by this Authority on | |

[ x ] the claims:

| | | | | |
|---|---|---|---|---|
| [ ] | pages | | | as originally filed/furnished |
| [ ] | pages* | | as amended (together with any statement) under Article 19 | |
| [ x ] | claims | 1 to 17 | received by this Authority on | May 27, 2005 |
| [ ] | pages* | | received by this Authority on | |

[ x ] the drawings:

| | | | | |
|---|---|---|---|---|
| [ x ] | pages | 1/12 to 12/12 | | as originally filed/furnished |
| [ ] | pages* | | received by this Authority on | |
| [ ] | pages* | | received by this Authority on | |

[ ] a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/figs

[ ] the sequence listing *(specify):*

[ ] any table(s) related to sequence listing *(specify):*

4. [ ] This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/figs

[ ] the sequence listing *(specify):*

[ ] any table(s) related to sequence listing *(specify):*

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

**Box No. II Priority**

1. [ ] This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   [ ] copy of the earlier application whose priority has been claimed (Rule 66.7(a)).

   [ ] translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. [ ] This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

The priority document has been found to provide support for claims 1 to 17, therefore, priority rights has been found valid (Rule 64.1).

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**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The question whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

[ ] the entire international application

[ x ] claims Nos. 15 to 17

because:

[ x ] the said international application, or the said claims Nos. 15 to 17
relate to the following subject matter which does not require an international preliminary examination *(specify):*

The subject matter of claims 15 to 17 relates to a method of medical treatment of the human or animal body (Rule 67.1 of the PCT). For the assessment of these claims on the question whether they are industrially applicable, no unified criteria exists in the PCT. The patentability can also be dependent upon the formulation of the claims. Certain national offices do accept claims worded as methods of medical treatment while others rather accept claims worded as use claims and would then recognize the industrial applicability for these claims. Under the PCT Rules, no industrial applicability can be acknowledged.

[ ] the description, claims or drawings *(indicate particular elements below)* or said claims Nos.
are so unclear that no meaningful opinion could be formed *(specify):*

[ ] the claims, or said claims Nos. are so inadequately supported
by the description that no meaningful opinion could be formed *(specify):*

[ ] no international search report has been established for said claims Nos.

[ ] a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

[ ] furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

[ ] furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

[ ] pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

[ ] a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

[ ] the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

[ ] See Supplemental Box for further details.

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**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 1 to 17 | YES |
| | Claims | none | NO |
| Inventive step (IS) | Claims | 1 to 17 | YES |
| | Claims | none | NO |
| Industrial applicability (IA) | Claims | 1 to 14 | YES |
| | Claims | none | NO |

2. Citations and explanations (Rule 70.7)

D1: US 4164505 (Krajca, K. E. et al.),
D2: CA 2471649 (Reaney, M. J.),
D3: CA 2393403 (Reaney, M. J.),
D4: US 6316645 (Sih et al. C. J.),
D5: Strocchi, Revue Francaise des Corps Gras (1969), 16(1), 3-13,
D6: Kepler, C. R. et al., J. Biol. Chem., (1967), vol. 242, No. 24, 5686,
D7: Segredos, A. N., Fette, Seifen, Anstrichmittel (1974), 76(1), 8-16,
D8: JP 03207824B2 (Shiraki, T. et al.),
D9: Igarashi, M. et al., Cancer Letters (Shannon, Ireland) (2000), 148(2), 173-179.

Novelty and Inventive step

Documents D1, D2 and D3 disclose a process for conjugating fatty acids (linoleic acids and linolenic acids) comprising treatment of the source of the linolenic or/and linoleic acid with a base and aqueous medium at a temperature between 160-220°C.

Documents D4, D5, D6 and D7 disclose compounds cis-9, trans-11, cis-15-octadecatrienoic acid and cis-9, trans-13, cis-15-octadecatrienoic acid.

Documents D8 and D9 disclose a use of the conjugated linolenic acids in the prevention and treatment of cancer.

No teaching in the prior art describes a composition comprised of a mixture of cis-9, trans-11, cis-15-octadecatrienoic acid and cis-9, trans-13, cis-15-octadecatrienoic acid in a ratio of 1:1 and a concentration between 30% and 90 % by weight relative to the weight of the composition. Consequently, the subject matter of claims 1 to 17 is novel in respect of the prior art as defined in the regulations (Rule 64.1- 64.3 PCT) and thus meets the requirements of Article 33(2) PCT.

None of the prior art documents indicates the composition comprised of a mixture of cis-9, trans-11, cis-15-octadecatrienoic acid and cis-9, trans-13, cis-15-octadecatrienoic acid in a ratio of 1:1. Therefore an inventive step can be acknowledged for claims 1 to 17 (Article 33(3) PCT).

Industrial applicability

Due to the potential use of the composition comprising conjugated linolenic acids of the invention in the prevention and treatment of cancer and for drying oil in varnishes, the subject matter of claims 1 to 14 is considered to be industrially applicable and thus fulfilling the requirements of Article 33(4) PCT.

**Box No. VII Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

The instant claim's pages are not numbered. Under Rule 11.7 of the PCT all the sheets contained in the international application shall be numbered in consecutive Arabic numerals and shall be centered at the top or bottom of the sheet.

Anti-carcinogenic properties of CLA have been well documented, as well as stimulation of the immune system. Administration of CLA inhibits rat mammary tumorogenesis, as demonstrated by Ha *et al.*, Cancer Res., 52:2035-s (1992). Ha *et al.*, Cancer Res., 50:1097 (1990), reported similar results in a mouse forestomach neoplasia model. CLA has also been identified as a strong cytotoxic agent against target human melanoma, colorectal and breast cancer cells *in vitro.* A recent major review article confirms the conclusions drawn from individual studies (Ip, Am. J. Clin. Nutr. 66(6):1523s (1997)). In *in vitro* tests, CLAs were tested for their effectiveness against the growth of malignant human melanomas, colon and breast cancer cells. In the culture media, there was a significant reduction in the growth of cancer cells treated with CLAs by comparison with control cultures. The mechanism by which CLAs exert anticarcinogenic activity is unknown.

In addition, CLAs have a strong antioxidative effect so that, for example, peroxidation of lipids can be inhibited (Atherosclerosis 108, 19-25 (1994)). CLA has been found to be an *in vitro* antioxidant, and in cells, it protects membranes from oxidative attack. In relation to other important dietary antioxidants, it quenches singlet oxygen less effectively than beta-carotene but more effectively than alpha-tocopherol. It appears to act as a chain terminating antioxidant by chain-propagating free radicals (U.S. Pat. No. 6,316,645 ).

Pharmaceuticals which have been used in clinical therapy include many agents such as anticancer agents, antibiotic substances, immunopotentiators, immunomodulators, etc. (such as alkylating agents antimetabolites and plant alkaloids) but it can be hardly said that such a drug therapy has been completely established already. An object of the present invention is to develop a substance having a physiological function such as apoptosis-inducing action.

Conjugated linoleic acid (CLA) is a general term used to name positional and geometric isomers of linoleic acid C18:2(9 *cis*,12 *cis*). It usually denotes a mixture of mainly two isomers: C18:2(9*cis*, 11*trans*) and C18:2(10*trans*,12*cis*). They are usually present in a 1:1 ratio and the sum of these two isomers can vary between 30% and 90%. The majority of CLA in nutraceutical market do not mention the accurate composition for the content of each isomer, but generally the product is around 80% for both isomers. The most important isomer in term of anti-cancer activity is the C18:2(9*cis*, 11*trans*) (Seidel *et al.*, 2001, Patent. 6,319,950, Liu *et al.*, 2002 (a, b), Roche *et al.*, 2002, Pariza *et al.*, 1991).

CLA have been suggested as useful as anti-cancer agents for treatment of cancer. The latest research reveals the most dramatic impact may be on the reduced risk and incidence of mammalian cancer (breast and colon cancer). It has been shown that CLA down-regulated

**References**

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27 MAY 2005 27-05-05

CLAIMS:

1. A process for the preparation of a composition comprising a mixture of linolenic acids, said linolenic acids being 9*cis*,11*trans*,15*cis*-octadecatrienoic acid and 9*cis*,13*trans*,15*cis*-octadecatrienoic acid and having a ratio of 1:1 w:w, a concentration of said mixture varying between 30% and 90% by weight relative to the weight of the composition, said process comprising the steps of:

- blending one or a mixture of vegetable oils with various concentrations of linolenic acid or partial glycerides of such oils or partially purified and/or concentrated isomers with a base and in the presence of water; and
- recovering the resulting conjugated linolenic acids.

2. The process according to claim 1, characterised in that it is performed at a temperature ranging from 160°C to 200°C.

3. The process according to claim 2, characterised in that the temperature is 180°C.

4. The process according to claim 1, characterised in that it proceeds for a period varying between 0.5 hour to 4 hours.

5. The process according to claim 4, characterised in that the period is 2 hours.

6. The process of claim 1, characterised in that the vegetable oil comprises linseed oil, *Plukenetia volubilis* oil, borage oil or a mixture thereof.

7. The process of claim 1, characterised in that the base is selected from a group consisting of sodium hydroxide, sodium alkoxylate, sodium metal, potassium hydroxide, potassium alkoxylate and potassium metal.

8. The process according to claim 7, characterised in that the base is potassium hydroxide or sodium hydroxide.

9. A composition comprising a mixture of linolenic acids, said linolenic acids being 9*cis*,11*trans*,15*cis*-octadecatrienoic acid and 9*cis*,13*trans*,15*cis*-octadecatrienoic acid, characterised in that said linolenic acids are present in a ratio of 1:1 w:w and said mixture varying between 30% and 90% by weight relative to the weight of the composition.

10. The composition according to claim 9, characterised in that it comprises at least 40% by weight of said mixture, and less than 0.5% by weight of 11,13-cyclic by-product.

11. Use of the composition according to claim 9, in a therapeutically effective amount for the prevention or treatment of cancer in a mammal.

12. The use according to claim 11, characterised in that the mammal is a human.

13. The use according to claim 11, characterised in that the cancer is breast cancer.

14. Use of the composition according to claim 9, for dying oil in varnishes.

15. A method for preventing or treating cancer in a mammal, comprising administering to a mammal a therapeutically effective amount of the composition according to claim 9.

16. The method of claim 15, characterised in that the mammal is a human.

17. The method of claim 15, characterised in that the cancer is breast cancer.